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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,815	06/06/2002	Takehiko Koide	06478.1461	2579

22852 7590 08/25/2004

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,815	KOIDE, TAKEHIKO	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 9, 2004 has been entered.

Claim 5 has been amended. Claims 2-9 are pending and are the subject of this Office Action.

DETAILED ACTION

1. Rejections

1.1. 35 USC, section 112, first paragraph

Lack of written description

Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with written description requirement. The reasons are stated in the previous Office Actions, of May 22, 2003, November 25, 2003 and March 2, 2004, and reiterated herein.

The claims are directed to a human antithrombin variant characterized in that at least one of the amino acids at positions 78, 278, 378 and 380 are changed. The claims are directed to a large genus of human antithrombin variants, but the specification fails to describe their structure. No single representative species of the genus is disclosed by presenting its amino acid sequence and its sequence identification number; neither the encoding gene of

the polypeptide is given. Therefore, one skilled in the art does not know what amino acid sequence is to be modified so that its amino acids in positions 78, 278, 378 and 380 are substituted. Applicants do not disclose the amino acid sequence of antithrombin III that they mutated. The claimed muteins should be identified not only by their function but also by their structure.

In their Remarks Applicants point out that the specification identifies natural antithrombin III as a main control factor in the blood coagulation system etc. (page 2 lines 21-25 of the specification) whereas the natural mutants quoted by the examiner are inactive. This argument is persuasive. However, none of the information on page 2 refers to the structure of the antithrombin III that was mutated by Applicants. None of the prior art that discloses human wild type antithrobin III is incorporated in the specification by reference, or even mentioned on page 2. The claimed muteins should be identified not only by their function but also by their structure, this however is not the case. The claims, therefore remain rejected for lack of written description of structure.

Applicants traverse this rejection in their Remarks of Response of August 9, 2004 stating, "Information which is well known in the art need not be described in detail in the specification; there is no need to disclose what is already known. MPEP §2163. The amino acid sequence of human antitrombin III is well known in the art. The Applicant himself published the amino acid sequence in 1994 in a globally distributed journal, The Journal of Biochemistry. See F. Tokunaga, T. Koide et al., Amino Acid Sequence of Porcine Antithrombin III, J. Biochem. 116: 1164-1170,1167 (1994). Furthermore, the specification makes reference to

Japanese Patent No. 262598/1990, corresponding to EP 0384112, which disclose the complete amino acid sequence of natural human antithrombin III. See Specification, page 4;...A copy of EP 0384122 was provided with the Information Disclosure Statement on December 21, 2001."

Applicants arguments have been fully considered but is found not persuasive for the following reasons. The article by Tokunaga and co-workers published in J. Biochem. presents porcine and not human antitrombin III; the amino acid sequences of both proteins are different. For example, the porcine protein does not have serine in position 380 and is shorter. On the other side, the EP034122 presents in Table 1 and amino acid sequence, presumed the human antitrombin III, which is not described in the document. In addition, the EP034122 is not incorporated by reference to the specification. Thus, the claimed inventions lacks structural description and the claims remain rejected.

3.4. 35 USC section 103

Claims 5 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huntington J. A. et al. (Mechanism of Heparin Activation of Antithrombin. Evidence for Reactive Center Loop Preinsertion with Expulsion upon Heparin Binding, *Biochemistry*, 1996, 35, 8495-8503, and Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277) and in view of common knowledge in molecular biology. The reasons were indicated in the previous Office Action, paper No. 10 and are reiterated herein.

Huntington et al. generated, by site directed mutagenesis, a variant of antithrombin wherein serine in position 380 is substituted by thryptophan (1996) or cysteine (1998); see the abstracts of both papers. Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33). On page 3274, left column line 9, Huntington et al. write: "We expressed a P14 S→C variant of antithrombin (S380C) to provide a means of introducing a bulky group at the P14 position by chemical modification and thus to lock the antithrombin in a conformation with the P14 residue exposed, rather than buried." The variants obtained by Huntington and co-workers indeed do not require heparin activation for its inhibitory function.

Huntington et al. do not teach substitution of residue 380 by other amino acids like alanine, aspartic acid, glycine, histidine, ileucine, leucine, asparagines, threonine, tyrosine, and valine that are recited in claim 5 and 9. However, it would have been obvious to one having ordinary skill in the art at the time of invention to have antithrombin and modify it to heparin independence by substituting the residue 380 by other amino acids particulary the ones which are bulky in comparison with serine, because the displacement of P14 from beta-sheet can be achieved by substitution of serine 380 by other bulky amino acid. Therefore, one skilled in the art would have use other amino acids than tryptophan and cysteine to produce other muteins with desired property, similarily as Huntington et al. previously did.

The motivation is provided by Huntington et al. who write, "This accounts both for the occurrence of thrombosis in patients whose antithrombin has a defect in heparin binding or activation and for the widespread clinical use of exogenous heparin as anticoagulant" (page 3272 of the 1998 paper, left column, line 20). Thus, one skilled in the art would be motivated to obtain antithrombin that is more clinically useful by making it independent on its activator, heparin, by mutating position 380 and thus exposing P14 using several amino acids, and screening for the mutants having required property of heparin independence. The expectation of success was very high, because Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33.), and Huntington et al. also teach how to achieve this displacement. The displacement can be achieved by substitution of serine 380 by other bulkier amino acids.

In summary, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing this rejection applicants write in their Remarks, page 6, second paragraph, "In determining bulkiness, Applicant has referenced the maximum with of amino acid side chains as a proxy for bulkiness, thereby providing an objective scale. See Niwa and Ogino, 'Multiple Regression Analysis of the Beta-Sheet Propensity of Amino Acids.' J of Mol. Struct. (1996) 155-160, at 157 (Exhibit 1). Tryptophan has a B5 value of 5.90. *Id.* Applicant has amended

claim 5 to delete Arg and Tyr, which have B5 values greater or equal to 5.90. Because Huntington II specifically identifies bulkiness as a functional aspects of the substitute amino acids used to create heparin independent antithrombins, a person skilled in the art would not have a reasonable expectation of success in substituting an amino acid less bulky than tryptophan."

Applicant's argument has been fully considered but is found not persuasive. Firstly, no Exhibit I is attached to Applicant's Amendment and Response of August 9, 2004. Secondly, although Huntington II specifically identifies bulkiness as a functional aspect of the substitute amino acids used to create heparin independent antithrombins, he himself obtain a heparin independent anithrombin by substitutin serine with cysteine, which is not bulkier than serine. In conclusion, a person skilled in the art would have a reasonable expectation of success in substituting serine in position 380 with any amino acid that is bulkier then serine. His, Ile, Leu, Pro, are certainly bulkier than serine. It is not clear, why the person skilled in art would not have a reasonable expectation of success in substituting position 380 with amino acid that is more bulky than serine but less bulky than tryptophan.

In the last Office Action the examiner indicated that obtaining an antithrombin by placing Ala, Gly and Thr in position 380 is not obvious, because these amino acid are not bulkier than the native serine. However claim 5 and 9 are not limited to muteins containing in position 380 any one of Ala, Gly and Thr.

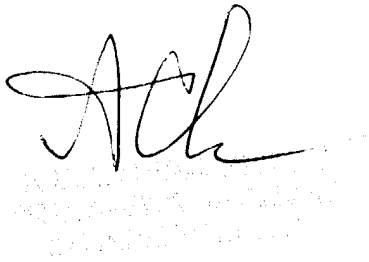
Conclusion

None of the claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.



Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner